UTS UNIVERSITY OF TECHNOLOGY SYDNEY

Development of a Surface-Enhanced Raman Spectroscopy Substrate for the Detection of Illicit Drugs in Oral Fluid

by Rhiannon Alder

Thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy (Science)

under the supervision of Professor Shanlin Fu, Dr Linda Xiao and Associate Professor Majid Ebrahimi Warkiani

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Certificate of authorship and originality

I, *Rhiannon Alder* declare that this thesis, is submitted in fulfilment of the requirements for the award of *Doctor of Philosophy (Science)* in the *Faculty of Science* at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

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Abbreviations

ANN	Artificial neural networks
ATS	Amphetamine type substances
CBD	Cannabidiol
CCD	Charged coupled device
CTAB	Cetyl trimethyl ammonium bromide
CV	Crystal violet
CVD	Chemical vapour deposition
DNA	Deoxyribonucleic acid
EBL	Electron beam lithography
EDS	Energy dispersive x-ray spectrometry
EF	Enhancement factor
EHT	Electron high tension
FT	Fourier Transform
FWHM	Full line width at half maximum intensity
GBD	Global burden of disease
GC-MS	Gas chromatography-mass spectrometry
$HAuCl_4$	Tetrachloroauric(III) acid

HPLC	High-performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
$KMnO_4$	Potassium permanganate
K-PLS	Kernel-partial least squares models
LC-MS	Liquid chromatography-mass spectrometry
LLE	Liquid-liquid extraction
LOQ	Limit of quantification
LSD	Lysergic acid diethylamide
MDMA	3,4-methylenedioxymethamphetamine
MLR	Multiple linear regression
NA	Numerical aperture
NBOMes	N-methoxy benzyl compounds
NC	Nanocubes
NIL	Nanoimprint lithography
NIR	Near infrared
NSL	Nanostencil lithography
NSW	New South Wales
OWL	On-wire lithography

PCA	Principal component analysis
PCR	Principal component regression
PDA	Polydopamine
PEI	polyethyleneimine
PDMS	Polydimethylsiloxane
PFDT	Perfluorodecanethiol
PLS	Partial least squares regression
RR	Resonance Raman
SEM	Scanning electron microscopy
SERRS	Surface-enhanced resonance Raman spectroscopy
SERS	Surface-enhanced Raman spectroscopy
SM	Single-molecule
SORS	Spatially offset Raman spectroscopy
SPE	Solid-phase extraction
SVM	Support vector machine
SWGDRUG	Scientific Working Group for the Analysis of Seized Drugs
TERS	Tip-enhanced Raman spectroscopy
THC	Δ-9-tetrahydrocannabinol

UV	Ultraviolet
UV-Vis	Ultraviolet-visible spectroscopy

Publications

The works labelled with an asterisk are included in this thesis.

Journal Articles

2018

Xiao, L, Alder, R, Mehta, M, Krayem, N, Cavasinni, B, Laracy, S, Cameron, S & Fu, S 2018, 'Development of a quantitative method for the analysis of cocaine analogue impregnated into textiles by Raman spectroscopy.', *Drug testing and analysis*, vol. 10, no. 4, pp. 761-767

2020

*Alder, R, Xiao, L, & Fu, S 2020, 'Comparison of commercial surface-enhanced Raman spectroscopy substrates for the analysis of cocaine.', *Drug testing and analysis*, DOI:10.1002/dta.2894

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Conference Presentations

2017

Rhiannon Alder, Shimpei Watanabe, Declan Stockdale, Linda Xiao, Yu Wong, Shanlin Fu, 'Development of a Raman spectroscopic method for the determination of illicit substances in seized materials', *9th Forensic & Clinical Toxicology Association Conference, Melbourne, Victoria, 19-22 November 2017*

2018

*Rhiannon Alder, Linda Xiao, Olga Shimoni, Xing Yi Ling and Shanlin Fu, 'Development of a Surface Enhanced Raman Spectroscopy Substrate for Illicit Drug Detection', *Australia and New Zealand Forensic Science Society 24th International Symposium, Perth, Western Australia, 9-13 September 2018*

2019

*Rhiannon Alder, Linda Xiao and Shanlin Fu, 'Surface enhanced Raman spectroscopy towards low level detection of drugs', *10th Forensic and Clinical Toxicology Association Conference, Adelaide, South Australia, 16-19th June 2019*

*Rhiannon Alder, Linda Xiao and Shanlin Fu, 'Detection of fentanyl and methamphetamine using surface enhanced Raman spectroscopy', *The 57th Annual Meeting of the International Association of Forensic Toxicologists, Birmingham, UK 2nd-6th September 2019*

Conference Poster

2019

*Rhiannon Alder, Linda Xiao, Shanlin Fu, 'Detection of illicit drugs in oral fluid by surface enhanced Raman spectroscopy', *Faculty of Science Transdisciplinary ECR Retreat, University of Technology Sydney 29th November 2019*

Abstract

Drug abuse is a worldwide issue which has led to an increasing need for on-site testing. Current on-site tests for illicit drugs are immunostrip devices which only test for a select number of analytes and require confirmatory laboratory testing. Raman spectroscopy is a non-destructive technique which when coupled with more sensitive Raman methods, such as surface-enhanced Raman spectroscopy (SERS), could allow for this technique to be used for the detection of illicit drugs at lower levels. This study investigated the development and use of SERS for the analysis of illicit drugs in oral fluid.

The first aim of the study was to benchmark commercially available SERS substrates for the analysis of illicit drugs. Seven commercially available SERS substrates were tested, and the substrate which enhanced the most analyte bands consistently was the JASMAT Ag substrate. The JASMAT Ag substrate was tested with several illicit drugs and their metabolites both as standards and extracted from oral fluid. All of the analytes, except THC, were able to be detected down to at least 10 ng/mL in standard solutions. The analytes extracted from oral fluid showed less analyte specific bands.

The second aim of the study was to use SERS for the quantification of methylamphetamine in oral fluid solutions. Two quantification methods were trialled for quantification; calibration curves using peak intensity and partial least squares regression (PLS). The PLS quantification attempts with oral fluid extraction samples revealed a negative interaction between the organic solvent and the JASMAT Ag SERS substrate. This resulted in an alternative pillar cuvette extraction method being trialled. The pillar cuvettes allowed for the tentative detection of methylamphetamine at a concentration of 100 ng/mL.

The third aim of the study was to develop a SERS substrate which was reproducible, cheap and able to enhance the analyte bands to the standard of the best performing commercial substrate. Many methods of SERS development were attempted, however, the only method which produced a reliable SERS substrate for illicit drug analysis was the plasma printing method. The 6 pass plasma printed substrate enhanced a similar number of bands to the JASMAT Ag substrate in the analysis of cocaine and fentanyl.

In conclusion, SERS has been shown to be a promising technology for the analysis of illicit drugs in oral fluid. This research has built foundations for the future development of an on-site collection, extraction and SERS device for oral fluid analysis of illicit drugs.